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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|--|-------------|----------------------|---------------------|------------------|
| 09/763,175 | 05/30/2001 | Hitoshi Kiyoi | 084335/0129 | 3517 |
| 7590 | 09/27/2005 | | | EXAMINER |
| Stephen B Maebius Foley & Lardner Suite 500 3000 K Street NW Washington, DC 20007-5109 | | | UNGAR, SUSAN NMN | |
| | | | ART UNIT | PAPER NUMBER |
| | | | 1642 | |
| DATE MAILED: 09/27/2005 | | | | |

Please find below and/or attached an Office communication concerning this application or proceeding.

| | | |
|------------------------------|------------------------|---------------------|
| Office Action Summary | Application No. | Applicant(s) |
| | 09/763,175 | KIYOI ET AL. |
| | Examiner | Art Unit |
| | Susan Ungar | 1642 |

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE three MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) Responsive to communication(s) filed on 18 July 2005.

2a) This action is **FINAL**. 2b) This action is non-final.

3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4) Claim(s) 1,6,7 and 9 is/are pending in the application.
4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5) Claim(s) _____ is/are allowed.

6) Claim(s) 1,6,7 and 9 is/are rejected.

7) Claim(s) _____ is/are objected to.

8) Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9) The specification is objected to by the Examiner.

10) The drawing(s) filed on _____ is/are: a) accepted or b) objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11) The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) All b) Some * c) None of:
1. Certified copies of the priority documents have been received.
2. Certified copies of the priority documents have been received in Application No. _____.
3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) Notice of References Cited (PTO-892)
2) Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date 1/5/05.

4) Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____.
5) Notice of Informal Patent Application (PTO-152)
6) Other: _____.

1. The Amendment filed July 18, 2005 in response to the Office Action of January 18, 2005 is acknowledged and has been entered. Previously pending claims 1 and 9 have been amended and claims 2-5, 8 and 10-11 have been canceled. Claims 1, 6-7 and 9 are currently under prosecution.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

3. The following rejections are being maintained:

Claim Rejections - 35 USC § 112

4. Claims 1, 6-7, 9 remain rejected under 35 USC 112, first paragraph for the essentially reasons previously set forth in the Paper mailed January 18, 2005, Section 7, pages 4-6.

Applicant argues that amendment of the claims to recite “a drug to treat blood cancer” and screening by “blood cells or hematopoietic stem cells” overcomes the rejection of claims 1-, 6-7, 9 and thus it would not require undue experimentation to carry out the invention of the present invention.

The argument has been considered but has not been found persuasive because Applicant has not addressed the issue drawn to lack of enablement for all blood cancers, does not address the issue drawn to lack of enablement to screen for a candidate compound for blood cancers that do not overexpress FLT3/ITD. Applicant does not respond to Examiner’s specific citation of the specification on page 3 wherein the inventors found that inhibition of FLT3/ITD mutations are found in AML patients and patients with myelodysplasia syndrome but not in patients with chronic myeloid leukemia or lymphocyte blood cancers. Applicant does not respond to Examiner’s specific citation of the specification at page 7 wherein the inventors teach that tumors targeted by the identified drug candidate,

screened by the instant method include any tumors caused by IDT of FLT3. Applicant does not respond to the citation of papers written by those of skill in the art that confirm the limited association of FLT/ITD with hematological tumors on page 6 of the action. Applicant's amendment of the claims as set forth above does not address the issues set forth previously and above and therefore does not overcome the rejection of record.

New Grounds of Rejection

Claim Rejections - 35 USC § 103

5. The following is a quotation of 35 U.S.C. § 103 which forms the basis for all obviousness rejections set forth in this Office action:

A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. Claims 1, 6-7 are rejected under 35 USC 103 as being unpatentable over Lemola et al (Blood, 1991, 77:1829-1836), of record in view of Kiyoi et al, of record, Yokota et al (Leukemia, 1997, 11:1605-1609), Carow et al (Blood, 1996, 87:1089-1096).

It is noted that the claim 1 is drawn to blood cells in which the FLT3/ITD gene has been introduced so as to express FLT3/ITD. Given that the ITD mutation is a mutation that is introduced in the cell, it is understood for

examination purposes that the subset of AML cells that comprise said mutation meet the limitations of the claim.

The claims are drawn to a method for screening a candidate compound for a drug to treat blood cancer comprising providing animal blood cells in which the FLT3/ITD gene has been introduced so as to express FLT3/ITD, wherein said cells proliferate cytokine independently, contacting said cells with a candidate compound and culturing the cells in the absence of cytokines and detecting the proliferation of said cells and selecting the compound that inhibits the proliferation of said cells by inhibiting FLT3/ITD function (claim 1), wherein said blood cancer is AML or myelodysplasia syndrome (claim 6), wherein said cytokine is IL-3 (claim 7).

Lemola et al, of record teach as set forth previously, to reiterate, Lemola et al teach a method for screening a candidate compound for an antitumor drug comprising contacting primary AML cells with said candidate drug and culturing said cells in the absence of cytokines (that is any cytokine including IL-3). Lemola et al teach as set for previously and above but do not teach a method for screening a candidate compound for a drug that inhibits FLT3/ITD function.

Kiyoi et al, of record teach that ITD is a novel modality of somatic mutation which constitutively activates FLT3 wherein the FLT3 is ligand independently phosphorylated.

Yokota et al teach that in cell samples from AML patients, 20% of the patients presented with blood cells comprising the IDT/FLT3 mutation (see abstract). Yokota et al further teach that the in-frame nature of these mutations strongly suggest that the abnormal protein product derived from this mutation functions dominantly and increases the growth of the leukemic cell (p. 1607, col

2). Yokota et al conclude that the mutation could play a crucial role in altering the function of FLT3 kinase and thus reinforcing proliferation of leukemic cells (p. 1609, col 1).

Carow et al teach the expression of both the short FLT3 and long form of FLT3, that is FLT3/IDT protein, in primary AML cells (see Fig. 3, page 1093, see especially the 130 kd and 160 kd forms) and teach that stimulation of these cells with ligand for FLT3 led to autophosphorylation of the FLT3 receptors, suggesting active signal transduction in these cells. The data suggests that overexpression of FLT3 may be involved in the maintenance/proliferation of malignant clones in cases of acute leukemia (p. 1095, col 2).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have substituted a method of screening for, and selecting, candidate drugs that inhibit FLT3 in both of its long and short forms and inhibits proliferation of AML cells because Yokoto et al specifically teaches that in-frame nature of these mutations strongly suggest that the abnormal protein product derived from this mutation functions dominantly and increases the growth of the leukemic cell, because Carow et al specifically teach that FLT3 forms are overexpressed in primary AML cells and are active phosphorylating molecules and because Kiyo et al, specifically teach that ITD is a novel modality of somatic mutation which constitutively activates FLT3 wherein the FLT3 is ligand independently phosphorylated. Given the teaching of Yokota et al wherein the data strongly suggests that the abnormal protein product derived from this mutation functions dominantly and increases the growth of leukemic cells, given the teaching of Kiyo et al that the ITD mutation results in the ligand independent constitutive activation of the kinase, it would reasonable to expect that the

inhibition of the abnormal protein product would be effective in reducing the proliferation of the leukemic cells. One would have been motivated to have substituted a method of screening for, and selecting, candidate drugs that inhibit FLT3 in both the long and the short form and inhibits proliferation of AMT cells in order to develop therapeutics that would be effective against AMT.

7. Claims 1, 9 are rejected under 35 USC 103 as being unpatentable over Lemola et al, of record in view of Kiyoi et al, *Supra*, Yokota et al, *Supra* and Carow et al, *Supra* and further in view of Li et al (PNAS, 1992, 89:3315-3319) and Nakao et al (Leukemia, 1996, 10:1911-1918).

The claims are drawn to a method for screening a candidate compound for a drug to treat blood cancer comprising providing animal blood cells in which the FLT3/ITD gene has been introduced so as to express FLT3/ITD, wherein said cells proliferate cytokine independently, contacting said cells with a candidate compound and culturing the cells in the absence of cytokines and detecting the proliferation of said cells and selecting the compound that inhibits the proliferation of said cells by inhibiting FLT3/ITD function (claim 1), wherein said cells are FDC-P1 cells. (claim 9).

Lemola et al, Kiyoi et al, Yokota et al, Carow et al teach as set forth above, but do not teach the introduction of the FLT2/ITD gene into FDC-P1 cells so as to express FLT3/ITD into FDC-P1 cells.

Li et al teach the conventional genetic engineering of FDC-P1 myeloid cells to express the receptor tyrosine kinase FGFR (see abstract) and further teaches that the cell line had previously been successfully used to express other isoforms of the receptor tyrosine kinase (p. 3315, col 2). The reference further teaches that most of the current knowledge of the effects of FGF's on the

stimulation of cellular proliferation and differentiation has been based on studies performed in primary cell cultures. The transient nature of such cell populations (i.e. the inability to maintain fully differentiated cells in culture) hindered effects to study the intracellular events that follow ligand binding and receptor activation (p. 3315, col 1). Thus the authors genetically engineered FDC-P1 in order to use this successful model as a model system for analyzing the function of FGFR in cell growth (p. 3315, col 1).

Nakao et al specifically teach the cDNA encoding FLT3/ITD.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have transfected or transformed the FDC-P1 cell line of Li et al with the construct of Yokota et al, 1996 to genetically engineer the cells to express FLT3/ITD and to substitute the engineered cells for the AMT cells of Lemola et al in the method of the combined references because Li et al specifically teach the transient nature of primary cell culture and the problems associated with assaying receptor tyrosine kinases in primary cell cultures. Further, it would have been *prima facie* obvious and one would have been motivated to specifically transform or transfect the FDC-P1 cell line with the long form of the FLT3 receptor tyrosine kinase because Yokota et al, 1997 specifically suggest that since the FLT3/ITD isoform functions for the proliferation of leukemic cells and Kiyoi et al specifically teach that the FLT3/ITD is constitutively activated. In addition, one would have been motivated to have transfected or transformed the FDC-P1 cell line of Li et al with the construct of Yokota et al, 1996 to genetically engineer the cells to express FLT3/ITD and to substitute the engineered cells for the AMT cells of Lemola et al in the method of the combined references in order to use a model

system that had already been shown to be successful for the assay of tyrosine receptor kinase with three different isoforms of a tyrosine receptor kinase.

8. All other objections and rejections recited in the previous Office Action are hereby withdrawn.

9. No claims allowed.

10. Applicant's amendment necessitated the new grounds of rejection.

Accordingly, **THIS ACTION IS MADE FINAL**. See M.P.E.P. § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 C.F.R. § 1.136(a).

A SHORTENED STATUTORY PERIOD FOR RESPONSE TO THIS FINAL ACTION IS SET TO EXPIRE THREE MONTHS FROM THE DATE OF THIS ACTION. IN THE EVENT A FIRST RESPONSE IS FILED WITHIN TWO MONTHS OF THE MAILING DATE OF THIS FINAL ACTION AND THE ADVISORY ACTION IS NOT MAILED UNTIL AFTER THE END OF THE THREE-MONTH SHORTENED STATUTORY PERIOD, THEN THE SHORTENED STATUTORY PERIOD WILL EXPIRE ON THE DATE THE ADVISORY ACTION IS MAILED, AND ANY EXTENSION FEE PURSUANT TO 37 C.F.R. § 1.136(a) WILL BE CALCULATED FROM THE MAILING DATE OF THE ADVISORY ACTION. IN NO EVENT WILL THE STATUTORY PERIOD FOR RESPONSE EXPIRE LATER THAN SIX MONTHS FROM THE DATE OF THIS FINAL ACTION.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Susan Ungar, PhD whose telephone number is (571) 272-0837. The examiner can normally be reached on Monday through Friday from 7:30am to 4pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew, can be reached at 571-272-0787. The fax phone number for this Art Unit is 571-273-8300.



SUSAN UNGAR, PH.D
PRIMARY EXAMINER

Art Unit: 1642

Susan Ungar
Primary Patent Examiner
September 21, 2005

*Signature
on previous page*